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1: Mol Cancer Ther. 2002 Oct;1(12):989-97.

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Inhibition of the phosphatidylinositol 3'-kinase-AKT pathway induces apoptosis in pancreatic carcinoma cells in vitro and in vivo.

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The phosphatidylinositol 3'-kinase (PI3k)-AKT survival pathway is activated in many malignancies. We observed constitutive AKT phosphorylation (on S473) consistent with pathway activation in seven of nine human pancreatic carcinoma cell lines in vitro. Exposure of the cells to two structurally distinct inhibitors of PI3k (worthmannin and LY294002) resulted in a dose-dependent induction of apoptosis in six of seven of the cell lines that displayed constitutive AKT phosphorylation but not in either of the cell lines that did not. The mitogen-activated protein/extracellular signal-regulated kinase kinase-mitogen-activated protein kinase inhibitor PD98059 also induced apoptosis in two of the cell lines, including one of the LY294002-insensitive lines (AsPC-1). Exposure of orthotopic L3.6pl pancreatic tumors to LY294002 resulted in dose-dependent inhibition of tumor growth, and decreased peritoneal and liver metastases, effects that were associated with an inhibition

transferase-mediated nick end labeling staining characteristic of apoptosis. Furthermore, a suboptimal dose of LY294002 (25 mg/kg) produced additive inhibition of tumor growth when combined with a suboptimal dose of gemcitabine (62 mg/kg). Together, our results establish that the PI3k/AKT pathway is constitutively activated in a majority of human pancreatic cancer cell lines and establish that the pathway is a promising target for therapeutic intervention.

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